

REMARKS

Claims 1-59 were pending in the application. Claims 3, 4, 14, 16, 17, 19, 20, 23, and 39 have been amended. Claims have been canceled without prejudice herein. Claims 7-10, 22-24, 33 and 41-59 have been cancelled as being drawn to a non-elected invention. New claims 60-68 have been added. Accordingly, claims 3, 4, 14-17, 19, 20, 23, 26, 27, 30, 39, 40, and 60-68 are currently pending.

Support for the amendments to the claims can be found in the application and/or claims as filed. Specifically, support for the phrase "at least an immunogenic portion of a cell surface receptor specifically expressed on the surface of activated B cells" can be found at least at page 4, line 4. Support for the phrase "immunologically cross-reactive with the autologous polypeptide" can be found at least at page 23, lines 12-15. Support for the phrase "at least one T helper cell epitope" can be found at least in previously pending claim 18. Support for the phrase "specifically expressed on the surface of cells targeted for elimination or reduction" can be found at least at page 3, line 5. Support for the phrase "reducing or eliminating the population of cells expressing the cell surface receptor" can be found at least in Examples 1 and 4. Support for new claim 60 can be found at least at page 20, line 2. Support for new claims 61 and 62 can be found at least in Example 1 and in previously pending claim 57. Support for new claims 63-65 can be found at least at page 26. Support for new claim 66 and 67 can be found at least at page 27.

No new matter has been added. The foregoing claim amendments should in no way be construed as an acquiescence to any of the Examiner's rejections, and have been made solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

The Pending Claims

The pending claims are directed to an immunogenic composition, comprising: a first polypeptide, which is autologous to a subject or which is immunologically cross-reactive with the autologous polypeptide, coupled to a second polypeptide, which is heterologous to the subject, wherein the first polypeptide comprises *an immunogenic portion of a polypeptide*

specifically expressed on the surface of activated B cells and wherein the second polypeptide contains at least one T helper cell epitope, the composition being capable of eliciting an immune response against B cells in the subject.

The claims are further directed to an immunogenic composition, comprising: a first polypeptide which is autologous to a subject or which is immunologically cross-reactive with the autologous polypeptide coupled to a second polypeptide which is heterologous to the subject, wherein the first polypeptide comprises *an immunogenic portion of a molecule selected from the group consisting of: CD79 α , CD79 β , and CD20* and wherein the second polypeptide comprises at least one T helper cell epitope, the composition being capable of eliciting an immune response against B cells in the subject.

The claims are still further directed to an immunogenic composition comprising a first polypeptide which is autologous to a subject or which is immunologically cross-reactive with the autologous polypeptide to the subject coupled to a second polypeptide which is heterologous to the subject, wherein the first polypeptide comprises *an immunogenic portion of a polypeptide specifically expressed on the surface of cells targeted for elimination or reduction* and the second polypeptide comprises at least one T helper cell epitope, and wherein the composition is capable of reducing or eliminating the population of cells expressing the cell surface receptor.

The claims are further directed to an immunogenic composition comprising a first polypeptide which is autologous to a subject or which is immunologically cross-reactive with the autologous polypeptide coupled to a second polypeptide which is heterologous to the subject, wherein the first polypeptide comprises *an immunogenic portion of a cell surface polypeptide specifically expressed on the surface of B cells* and the second polypeptide comprises at least one T helper cell epitope, the composition being capable of eliciting an immune response against B cells in the subject.

Rejection of claims 1-6, 11-21, 25-32, and 34-40 Under 35 U.S.C. 112, first paragraph

Claims 1-6, 11-21, 25-32, and 34-40 have been rejected under 35 U.S.C. 112, first paragraph. It is the Examiner's position that the specification does not reasonably provide enablement, e.g., for "any immunogenic composition comprising any 'first polypeptide' coupled to any 'second polypeptide' wherein the second polypeptide is heterologous to a subject, the composition being capable of eliciting any immune response against any autologous antigen in the subject." The

Examiner also states that "[t]he specification discloses only four fusion proteins selected from the group consisting of (1) mouse Ig fused to human IgG Fc, (2) CD79 α fused to the Fc region of IgG1 and (3) CD79 β fused to fused to the Fc region of IgG1 and mouse CD20 fused to human IgG Fc for making autoantibody to the Ig, CD79 α , CD79 β and CD20 expressed by B cell[s], respectively."

The Examiner also states that the specification does not provide sufficient information regarding the structure or function of the claimed compositions. This rejection is respectfully traversed.

The subject matter of the pending claims is set forth above. With respect to the first polypeptide, the claims require that the first polypeptide be autologous to a subject or immunologically cross-reactive with the autologous polypeptide and that it be: i) *an immunogenic portion of a polypeptide specifically expressed on the surface of activated B cells*; ii) *an immunogenic portion of a molecule selected from the group consisting of: CD79 α , CD79 β , and CD20*; iii) *an immunogenic portion of polypeptide specifically expressed on the surface of cells targeted for elimination or reduction*; or iv) *an immunogenic portion of a polypeptide specifically expressed on the surface of B cells*. With respect to the second polypeptide, the claims require that it be heterologous to the subject and comprise at least one T helper cell epitope.

In order for a claimed invention to be enabled, the standard is not whether or not experimentation is necessary to practice the claimed invention. Rather, the standard is whether or not the experimentation necessary to practice the claimed invention is undue (See *In re Wands*, 858 F.2d at 737). Thus, enablement is not precluded by the necessity for some experimentation, and a considerable amount of experimentation is permitted. *In re Wands*, supra.

Applicants provide sufficient guidance such that one of ordinary skill in the art could practice the methods claimed in the claims without undue experimentation. For example, Applicants teach numerous examples of polypeptides appropriate for use as the first and second polypeptides of the invention. In addition, Applicants provide numerous examples of cell surface molecules that could be used to make the claimed immunogenic compositions. For example, the specification teaches that molecules such as TNFR, IL-4R, IL-12R, IL-2R, EGFR, PDGFR, bombesin receptor, CTLA4, CD3, membrane Ig, TCR, and FCR, CD81, CD21, CD19, CD79, CD32, CD80, CD86, CD40, CD11a/CD18, CC22, CD45, CD28, CD2, CD4, CD8, CD154, CD54, CD43, CD45.RO, CD64, CD46, CD56, and CD95, CD79 α , CD79 β , CD20, and CD19 can be used. In addition, other such molecules were known in the art and, therefore, need not be taught in the

specification. For example, other exemplary B cell surface molecules include CD32, CD35, CD18, CD11a, and Class II.

As required by the claims, the immunogenic composition must be capable of eliciting an immune response against an autologous polypeptide in the subject. The ability of the first polypeptide of the composition to elicit an immune response against the autologous polypeptide of the subject can be readily tested using techniques known in the art. For example, as taught at page 38 of the application art recognized techniques such as anti-autologous antibody production, T cell proliferation, cytokine production, or T cell cytotoxicity can be measured. Moreover, many antibodies that recognize cell surface molecules are known in the art. In addition to the forms of molecules taught in the specification, these art recognized immunogens, previously tested for their ability to induce antibodies that bind to molecules expressed on the cell surface, can be used in connection with the instant invention.

With respect to second polypeptides, applicants teach that such polypeptides are heterologous to a subject and comprise at least one T helper cell epitope. Thus, the pending claims do not embrace portions of polypeptides of as little as one amino acid. Whether or not a polypeptide comprises a T helper cell epitope can be readily tested using techniques that are known in the art. For example, one of skill in the art can assay for the presence of T cell epitopes in a polypeptide using art recognized methods such as measuring the ability of the polypeptide to stimulate T cells in vitro using standard techniques (see e.g., Gogolak et al. 200 Biochem. Biophys. Res. Comm. 270:190; Attached as Appendix A). Alternatively, art recognized techniques employing computer programs which identify T cell epitopes can be used, e.g., EpiPlot 1.0; epiMer/Optimer; AMPHI; or SOHHA.

The Examiner further states that "[w]ith regard to claim 19, the term 'comprises' is open-ended. It expands the second polypeptide to include additional amino acid residues at either or both ends of a portion of any undisclosed 'second polypeptide'." Although the claimed compositions can comprise additional amino acid sequences, the claims also require that they function to induce an immune response to an autologous polypeptide in a subject. Accordingly, the claims do not embrace compositions that do not induce this result. Whether or not a composition induces an immune response against an autologous polypeptide is readily testable using methods described in the specification and/or methods known to those of skill in the art. For example, immunogenic compositions

within the scope of the claims which also include additional amino acid sequences have been made and tested for their ability to induce an immune response to an autologous polypeptide. For example, a reference by Huang et al. (Immunology Letters 81:49; Attached as Appendix B) uses the methods taught in the instant application and shows that flexible hinge region polypeptides can be included in the compositions of the invention.

Applicants further argue that it is within the skill of the art to determine which first polypeptides would be useful and effective as part of a pharmaceutical composition based on their expression on a cell targeted for reduction or elimination. For example, many disorders or conditions were known in the art to be associated with B cells. For example, allergic disorders or autoimmune disorders involving antibody production. Similarly, other cell surface molecules are known in the art to be expressed on certain cells that it may be desirable to target for reduction or elimination, e.g., tumor cell surface molecules for reduction or elimination of cancer cells (e.g., molecules recognized by the Y2B8, Lym 1, Lym 2, LL2, Her2, B1, MB1, BH3, B4, B72.3, or 5E10 antibodies known in the art) or immune cell surface molecules for reduction or elimination of immune cells to reduce an unwanted or pathological immune response. Accordingly, given the teachings of the instant application, one of ordinary skill in the art could readily select a molecule expressed on the surface of cells and make a construct within the scope of the claims.

With respect to specific constructs exemplified, in one embodiment, Applicants teach that Ig fusion proteins can be made. In contrast to the comments made by the Examiner, Applicants do not disclose only four different fusion proteins. While Applicants may provide working examples of several specific fusion proteins, the disclosure of the application is not limited to these fusion proteins. Applicants teach numerous examples of cell surface molecules that can be made as fusion proteins to produce the claimed compositions.

Applicants also provide working examples of the effectiveness of exemplary immunogenic compositions within the scope of the claims. Specifically, Applicants teach that constructs comprising an immunogenic portion of Ig α , Ig β , or CD20 are each effective in inducing an immune response against the cells expressing these molecules. The results obtained using CD20 constructs described in Example 4 are detailed in an article published in Immunology Letters (2002 81:49), attached as Appendix B. The working examples and later published references show that the claimed compositions

induce an immune response to autologous polypeptides expressed on the surface of cells and result in a reduction in the numbers of cells expressing these molecules. The fact that such varied molecules can serve as targets indicates that the first polypeptide need only be derived from a polypeptide expressed on the surface of a cell.

In addition, the Examiner appears to doubt whether the claimed immunogenic compositions would be useful for the claimed utility. Applicants dispute this contention and note that the specification provides evidence from an in vivo experiment that shows that the concentration of cells expressing the cell surface polypeptide can be reduced. Applicants note that under 35 U.S.C. §112, first paragraph, the Examiner has the "initial burden of setting forth a reasonable explanation as to why the scope of protection provided by [the claims] is not adequately enabled by the description of the invention provided in the specification." *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993). Specifically, in *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995), it was held that:

Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility.

Additionally, the court stated that in the absence of a reason to doubt the objective truth of the teachings contained in the specification, the methods of making and using the claimed invention must be taken as complying with the requirements of §112, first paragraph. The Examiner has not met this burden, accordingly, the claims must be taken as complying with §112, first paragraph.

In view of the foregoing, it is clear that one of ordinary skill in the art, armed with the knowledge of one of the ordinarily skilled artisan and given the teachings and methods disclosed in Applicants specification, would be able to make and use the claimed immunogenic compositions using no more than routine experimentation.

Accordingly, Applicants submit that the claimed invention is fully enabled by the disclosure in Applicants' specification and respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

Rejection of claims 1-6, 11-21, 25-32, and 34-40 Under 35 U.S.C 112, first paragraph

Claims 1-6, 11-21, 25-32, and 34-40 have been rejected under 35 U.S.C 112, first paragraph. The Examiner contends, e.g., that "[t]he specification does not reasonably provide a written description of, e.g., *any* immunogenic composition comprising *any* "first polypeptide" coupled to *any* "second polypeptide" wherein the second polypeptide is heterologous to a subject, the composition being capable of eliciting any immune response against *any* autologous antigen in the subject." The Examiner further states that "[t]he specification discloses only Ig from human and mouse Ig, CD79 α , CD79 β and CD20 expressed by B cell" and that "one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus."

The subject matter of the pending claims is set forth above. With respect to the first polypeptide, the claims require that the first polypeptide be autologous to a subject or immunologically cross-reactive with the autologous polypeptide and that it be: i) *an immunogenic portion of a polypeptide specifically expressed on the surface of activated B cells*; ii) *an immunogenic portion of a molecule selected from the group consisting of: CD79 α , CD79 β , and CD20*; iii) *an immunogenic portion of polypeptide specifically expressed on the surface of cells targeted for elimination or reduction*; or iv) *an immunogenic portion of a polypeptide specifically expressed on the surface of B cells*. With respect to the second polypeptide, the claims require that it be heterologous to the subject and comprise at least one T helper cell epitope.

Applicants note that "[a] specification may, within the meaning of 35 U.S.C., § 112, First Paragraph, contain a written description of a broadly written claimed invention *without describing all species that claim encompasses*." *Utter v. Hiraga*, 845 F.2d 993, 6 USPQ2d 1709 (Fed. Cir. 1988). Applicants have described a genus of immunogenic compositions based on the requirement that they comprise a first polypeptide that is autologous to a subject or immunologically cross-reactive with the autologous polypeptide and a second polypeptide that is heterologous to the subject and comprises a T helper cell epitope.

Exemplary cell surface molecules described in the specification include, e.g., TNFR, IL-4R, IL-12R, IL-2R, EGFR, PDGFR, bombesin receptor, CTLA4, CD3, membrane Ig, TCR, and FCR, CD81, CD21, CD19, CD79, CD32, CD80, CD86, CD40, CD11a/CD18, CC22, CD45, CD28, CD2, CD4, CD8, CD154, CD54, CD43, CD45.RO, CD64, CD46, CD56, and CD95, CD79 α , CD79 β , CD20, and CD19. Although working examples in the application included CD79 α , CD79 β , and CD20, applicants note that an embodiment of an invention need not be

present in a working example in order to be described.

Structural information for specific molecules that can be used in the claimed compositions was known in the art at the time the application was filed. For example, the sequences of exemplary molecules were known to those of ordinary skill in the art and/or were available, e.g., through GenBank or, e.g., The Leucocyte Antigen Facts Book, 1997, A. N. Barclay et al. Academic Press Limited. The claimed requirement that the first polypeptide be autologous to a subject or immunologically cross-reactive with the autologous polypeptide and a second polypeptide be heterologous to the subject and comprise a T helper cell epitope. This functional description coupled with the known structure of suitable cell surface molecules is sufficient to satisfy the requirements of 35 USC §112. Thus, the instant specification satisfies the written description requirement for the claimed invention as set forth in the Written Description Guidelines (66 Fed. Reg at 1106) and by the court in *Enzo Biochem, Inc. v. Gen-Probe Inc.* (296 F.3d 1316 (Fed. Cir. 2002)). Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this section 112, first paragraph rejection of the pending claims.

Rejection of Claims 1-4, 14, 16, and 18 Under 35 U.S.C. 102(b)

Claims 1-4, 14, 16, and 18 have been rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,837,268. It is the Examiner's position that the '268 patent teaches an immunogenic composition comprising a first polypeptide such as autologous polypeptide (self) [gonadotropin releasing hormone] GnRH coupled to or fused to a second polypeptide such as heterologous polypeptide (non-self) leukotoxin to the subject wherein the reference second polypeptide in the composition is capable of eliciting and enhancing the immune response such as antibody against the reference autologous (endogenous or self) antigen GnRH." This rejection is respectfully traversed.

The subject matter of the amended claims is set forth above. The teachings of the '268 patent are limited to the use of gonadotropin releasing hormone conjugated to leukotoxin. As taught in the '268 patent, endogenous proteins may be rendered effective autoantigens by multimerization of their epitopes. Gonadotropin releasing hormone is not *a polypeptide specifically expressed on the surface of activated B cell or B cells*. Gondotropin releasing hormone is not *a polypeptide specifically expressed on the surface of cells targeted for elimination or reduction*. In fact, GnRH is not a cell surface molecule at all. In addition, Gondotropin releasing hormone is also not *selected from the group consisting of: CD79 α , CD79 β , and CD20*. Accordingly, it is

respectfully requested that the rejection of claims 1-4, 14, 16, and 18 under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,837,268 be reconsidered and withdrawn.

Rejection of Claims 1-4, 14, 19 and 39 Under 35 U.S.C. 102(b)

Claims 1-4, 14, 19 and 39 have been rejected under 35 U.S.C. 102(b) as being anticipated by Nissim *et al* (EMBO J 10(1): 101-107, 1991; PTO 892). It is the Examiner's position that Nissim *et al* teach "an immunogenic composition comprising a first autologous polypeptide such as a self mouse IgE CH3 domain or homolog thereof such as CH3 coupled to a second heterologous polypeptide such as a portion of human IgE Fc region CH1, CH2 and CH4 domains of an immunoglobulin molecule (See page 102, chimeric human-mouse IgE, Fig 1, page 103, column 1, first paragraph, in particular) in cell culture medium (see page 107, Immunoassays and binding assays for IgE, in particular)." This rejection is respectfully traversed.

The subject matter of the amended claims is set forth above. Nissim *et al.* teaches murine-human chimeric IgE molecules, e.g., human IgE molecules comprising murine CH2 and/or CH3 domains. IgE is expressed on the surface of some B cells and is present in soluble form in the circulation. Because it is expressed both on cells and in the circulation, it is not a *polypeptide specifically expressed on the surface of B cells or activated B cells* as required by the claims. Furthermore, as IgE is present both in on the surface of some B cells and in the circulation, it is not a *polypeptide specifically expressed on the surface of cells targeted for elimination or reduction*. IgE is also not *selected from the group consisting of: CD79 α , CD79 β , and CD20*. Accordingly, it is respectfully requested that the rejection of claims 1-4, 14, 16, and 18 under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,837,268 be reconsidered and withdrawn.

Rejection of Claims 1-4, 14, 18-19, 37 and 39-40 Under 35 U.S.C. 102(b)

Claims 1-4, 14, 18-19, 37 and 39-40 have been rejected under 35 U.S.C. 102(b) as being anticipated by US Patent 5,653,980. The Examiner contends that the '980 patent teaches "an immunogenic composition comprising a first polypeptide such as the CH1 domain of IgE from mammalian species such as human and rat fused to a second polypeptide such as the entire sequence or part thereof of the constant CH2-CH3 domains of IgE that lacks the CH1 domain from mammalian species such as human and rat and wherein the reference IgE domains are mutually exchange[d] (self versus non-self) and further fused to glutathione-S-transferase (S. j26) from *S. japonicum* which is a

T helper epitope (See column 4, lines 21-26, column 9, lines 22-26, in particular).” This rejection is respectfully traversed.

The subject matter of the amended claims is set forth above. The '980 patent teaches the use of the CH2 and CH3 domains of IgE fused to a heterologous carrier protein to stimulate an immune response to IgE. IgE is expressed on the surface of some B cells and is present in soluble form in the circulation. Accordingly, it is not a *polypeptide specifically expressed on the surface of B cells or activated B cells* as required by the claims. As IgE is present both in on the surface of some B cells and in the circulation, it is not a *polypeptide specifically expressed on the surface of cells targeted for elimination or reduction*. IgE is also not *selected from the group consisting of: CD79 α , CD79 β , and CD20*. Accordingly, it is respectfully requested that the rejection of claims 1-4, 14, 16, and 18 under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,837,268 be reconsidered and withdrawn.

Rejection of Claims 3, 5-6, 11-15 and 17 Under 35 U.S.C. 103(a)

Claims 3, 5-6, 11-15 and 17 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Nissim *et al* (EMBO J 10(1): 101-107, 1991; PTO 892) or US Pat NO. 5,653,980 (Aug 1997; PTO 892) each in view of Hashimoto *et al* (Immunogenetics 40: 287-295, 1994; PTO 892) or Kooten *et al* (Clin Exp Immunol 110: 509-515, 1997; PTO 892). This rejection is respectfully traversed.

The Examiner relies on the teachings of Nissim *et al* and the '980 patent as set forth above. The Examiner relies on the teachings of Hashimoto *et al* as teaching “a polypeptide such as human and mouse CD79 α (Ig- α /mb-1) that is a B cell-associated antigen that forms heterodimer with CD79 β to become a B cell surface receptor (See page 287, column 2, page 288, Figures 1&2, in particular).” The Examiner relies on Kooten *et al* as teaching that “CD79 α (Ig- α /mb-1) and Ig- β (B29 or CD79 β) together form the B cell receptor and play a critical role in the development of B cells (See page 509, column 1, first paragraph, in particular).”

The Examiner states that one having ordinary skill in the art would have been motivated to make the claimed invention “because Hashimoto *et al* teach human CD79a (Ig-a/mb-1) forming complex with CD79P is critical for both cell surface expression and signaling functions of the B cell receptor (BCR) (See page 287, column 2, in particular)” and because the '980 patent “teaches that

domain swapping such as human IgE for rat or IgE and by coupling of one's own protein to a non-species specific protein, one can circumvent induction of tolerance to self IgE and give help to B-cells producing antibodies against a species specific antibodies (See column 5, lines 16-25, in particular)." The Examiner further states that Kooten *et al* "teach that that the CD79 α (Ig-a/mb-1) and Ig- β (B29 or CD79P) B cell receptor can be used for negative selection processes to eliminate B cells with specificity for autoantigens (See page 510, column 1, first paragraph, in particular)" and that Nissim *et al* teach "a self-polypeptide coupled to a non-self polypeptide could form an immunogenic composition (See page 102, chimeric human-mouse IgE, Fig 1, page 103, column 1, first full paragraph, in particular)."

The subject matter of the pending claims is set forth above. At the time the invention was made, there was no motivation to make the claimed invention, nor was there any reasonable expectation of success that one would succeed in making the claimed invention.

To establish a *prima facie* case of obviousness for the claimed invention, there must have been some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in the manner proposed by the Examiner. Second, there must have been a reasonable expectation of success at the time the invention was made. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See M.P.E.P. 2143. The prior art must suggest "to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process" and "[b]oth the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical Co.* 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988).

Nissim *et al.* teaches murine-human chimeric IgE molecules, e.g., human IgE molecules comprising murine CH2 and/or CH3 domains. The teachings of this reference are limited to the investigation of the portion of the Ig molecule necessary to bind to rodent Fc ϵ R1.

The '980 patent teaches the use of the CH2 and CH3 domains of IgE fused to a heterologous carrier protein to stimulate an immune response to IgE. The patent further teaches that the compositions described therein are useful in binding to the free pool of IgE circulating in the body (see Column 5, lines 1-3). Therefore, the reference teaches only induction of an immune response to polypeptides in the circulation and teaches that the mechanism by which the induced auto-antibodies to IgE work is by blocking the binding of IgE to Ig ϵ R on mast cells (see Column 5, lines 1-3).

Because IgE is present in the circulation, neither of these references teaches an autologous polypeptide specifically expressed on the surface *B cells or activated B cells, a polypeptide specifically expressed on the surface of cells targeted for elimination or reduction*, or a molecule selected from the group consisting of: *CD79 α , CD79 β , and CD20*.

Hashimoto et al. teach the chromosomal localization, genomic structure, and allelic polymorphism of the human CD79 α gene. Although the reference teaches that CD79 α is expressed on B cells during certain stages of development, at the time the invention was made, there was no motivation in the art to combine the teachings of Hashimoto et al. with those of the primary references. The '980 patent only taught enhancing immune responses using chimeric molecules made from IgE molecules which are expressed in the circulation. IgE acts by binding to IgE α R on mast cells and, as taught in the '980 patent, antibodies made against the region of self IgE that binds to the IgE α R results in inhibition of binding of IgE to IgE α R on mast cells. Based on these teachings of the '980 with respect to the generation of antibodies against IgE molecules in the circulation and the mechanism by which such antibodies work to block binding of IgE to the IgE α R on mast cells and the teachings of Hashimoto et al. with respect to the chromosomal localization and genomic structure of CD79 α , one of ordinary skill in the art would not have been motivated to make the claimed invention which induces an immune response to cells bearing a cell surface polypeptide. Moreover, the ordinarily skilled artisan would not have had a reasonable expectation of success in reducing or eliminating cells bearing the first polypeptide based on the teachings with respect to circulating IgE in the '980 patent.

The teachings of Kooten et al. fail to make up for the deficiencies in the primary references. Kooten et al. teach that a monoclonal antibody against Ig- β can be used to study B cell receptor signaling. In addition, the reference teaches that "[t]he combination of CD40 and antigen receptor-triggering induced strong proliferation early on, followed by massive cell death which could be prevented by IL-4." The reference states that "cross-linking of Ig- β could result in both positive and negative signals, dependent on additional signals present." Thus, in contrast to the suggestion made by the Examiner, the reference does not teach that signaling via Ig- β alone leads to negative selection of B cells; it requires signaling via CD40 and can be prevented by other signals. The reference further states that this represents a model for studying negative selection in mature B cells and fails to teach or suggest the use of Ig- β as a target for elimination of B cells, let alone using compositions such as those presently being claimed.

Based on these teachings of the '980 patent which are limited to inducing an

immune response to IgE in the circulation and the teaching of Kooten et al. that signaling via Ig- β can be either positive or negative, one of ordinary skill in the art would not have been motivated to make the claimed invention. With respect to motivation to make the claimed invention, the Examiner has failed to set forth adequate evidence of a motivating force which would have *impelled* one of ordinary skill in the art to modify the teachings of the references to arrive at the claimed invention. In support of their position, Applicants point to the CAFC decision in *In re Rouffet*, (149 F.3d 1350) (Fed. Cir. 1998)). Rouffet filed a patent application directed to technology to reduce signal transmission and receptor interruptions in the transmission signals from satellites. Rouffet taught changing the shape of the beam transmitted by the satellite's antenna to a fan-shaped beam. The Examiner rejected Rouffet's claims as unpatentable over U.S. patent number 5,199,672 (King) in view of U.S. Patent number 4,872,015 (Rosen) and a report titled "A Novel Non-Geostationary Satellite Communications System" (Ruddy). The CAFC found that:

[although] the board did not err in finding that the combination of King, Rosen, and Ruddy contains all of the elements claimed in Rouffet's application. . .the Board reversibly erred in determining that one of skill in the art would have been motivated to combine these references in a manner that rendered the claimed invention obvious. Indeed, the Board did not identify any motivation to choose these references for combination.

Similarly, it is Applicants' position that the Examiner has failed to point to any motivation to alter the teachings in the art to arrive at the invention as presently claimed. In *Rouffet* the Court of Appeals continued:

*[b]ecause the Board did not explain the specific understanding or principle within the knowledge of a skilled artisan that would motivate one with no knowledge of Rouffet's invention to make the combination, this court infers that the examiner selected these references with the assistance of hindsight. This court forbids the use of hindsight in the selection of references that comprise the case of obviousness. See In re Gorman, 933 F.2d 982, 986, 18 U.S.P.Q. 2D (BNA) 1885, 1888 (Fed Cir. 1991). Lacking a motivation to combine references, the Board did not show a proper prima facie case of obviousness. This court reverses the rejection over the combination of King, Rosen, and Ruddy. In re Rouffet at [*17].*

Since the Examiner has not pointed to any teaching or suggestion in the art that would have impelled the ordinarily skilled artisan to modify the cited art to arrive at the screening methods claimed, it is Applicants' position that the Examiner has used Applicants' invention as a blueprint to combine the references. The CAFC has ruled that "[a] holding that combination claims are invalid based merely upon finding similar elements in separate prior art patents would be 'contrary to statute and would defeat the congressional purpose in enacting Title 35.' " *SmithKline Diagnostics*, 859 F.2d. at 886-887 (citing *Panduit Corp v. Dennison Mfg. Co.*, 810 F.2d 1561, 1577 (Fed. Cir. 1987)) (citations omitted).

Moreover, the ordinarily skilled artisan would not have had a reasonable expectation of success in using the claimed compositions to reduce or eliminate cells expressing Ig- β given the teachings with respect to circulatory IgE in the '980 patent. This is especially true given the teachings of the Kooten reference that signaling via Ig β is insufficient to induce negative selection in B cells in the absence of CD40 signaling and that other signals can overcome any negative signal induced by Ig β .

In view of the foregoing, it is respectfully requested that the rejection of claims 3, 5-6, 11-15 and 17 under 35 USC §103(a) be reconsidered and withdrawn.

Rejection of Claims 3, 16 and 19 Under 35 U.S.C. 103(a)

Claims 3, 16 and 19 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Nissim *et al* (EMBO J 10(1): 101-107, 1991; PTO 892) or US Pat NO. 5,653,980 (Aug 1997; PTO 892) each in view of US Pat 5,225,538 (July 1993; PTO 892). This rejection is respectfully traversed.

The Examiner relies on the teachings of Nissim *et al* and the '980 patent as set forth above. The Examiner relies on the '538 patent as teaching "a composition comprising a first polypeptide such as mouse LHR fused to (See column 15, line 32, in particular) or chemically crosslink[ed] with crosslinking agent such as hydroxysuccinimide ester (See column 21, lines 49-61, in particular) to the Fc portion such as the CH2 and CH3 domains of human immunoglobulin such as IgG-1, IgG2, IgG3 or IgG4 (See column 10, lines 20-24, column 14, lines 40-41, column 46, line 35, in particular). The '538 patent teaches the Fc fusion protein improves the in vivo half of the reference fusion molecule (See column 14, lines 66-67, in particular)." The Examiner states that one having ordinary skill in the art would have been motivated to make the claimed invention "because the '538 patent teaches the Fc fusion protein

improves the in vivo half of the reference fusion molecule (See column 14, lines 66-67, in particular).”

The subject matter of the pending claims and the legal requirements for establishing obviousness are set forth above. At the time the invention was made, there was no motivation to make the claimed invention, nor was there any reasonable expectation of success that one would succeed in making the claimed invention.

As set forth above, Nissim et al. teaches murine-human chimeric IgE molecules, e.g., human IgE molecules comprising murine CH2 and/or CH3 domains. The teachings of this reference are limited to the investigation of the portion of the Ig molecule necessary to bind to rodent FcεR1. As set forth above, the ‘980 patent teaches the use of the CH2 and CH3 domains of IgE fused to a heterologous carrier protein to stimulate an immune response to IgE. The patent further teaches that the compositions described therein are useful in binding to the free pool of IgE circulating in the body (see Column 5, lines 1-3). Therefore, the reference teaches only induction of an immune response to polypeptides in the circulation and teaches that the mechanism by which the induced auto-antibodies to IgE work is by blocking the binding of IgE to IgεR on mast cells (see Column 5, lines 1-3). Neither of these references teaches an autologous polypeptide specifically expressed on the surface *B cells or activated B cells, a polypeptide specifically expressed on the surface of cells targeted for elimination or reduction*, or a molecule selected from the group consisting of: *CD79α, CD79β, and CD20*.

The teachings of the ‘538 patent fail to make up for the deficiencies in the primary references. The ‘538 patent teaches lymphocyte homing receptor/immunoglobulin fusion proteins. The reference teaches that the fusion proteins described therein have a longer half-life and can be purified using protein A. The patent describes the use of the fusion proteins both in vitro and in vivo. However, the ‘538 patent fails to teach or suggest that the compositions described therein induce an immune response against the lymphocyte homing receptor in a subject. In fact, the patent teaches that the immunoglobulin fused to the lymphocyte homing receptor is preferably “a human immunoglobulin when the variant is intended for in vivo therapy for humans.” See column 15, lines 29 -30. The patent also teaches that when making a fusion protein “[i]f the transmembrane and cytoplasmic domains are deleted one avoids the introduction of potentially immunogenic epitopes, either by exposure of otherwise intracellular polypeptides that might be recognized by the body as foreign or by insertion of heterologous polypeptides that are potentially immunogenic.” See Column 19, line 65 to Column 20, line 2. Thus, the reference actually teaches away from compositions designed to induce an autoimmune response.

Accordingly, based on the teachings of the '980 patent that are limited to IgE in the circulation and the teaching of the '538 patent that induction of an immune response to fusion proteins is not desirable in vivo, one of ordinary skill in the art would not have been motivated to make the claimed invention.

In view of the foregoing, it is respectfully requested that the rejection of claims 3, 16, and 19 under 35 USC §103(a) be reconsidered and withdrawn.

Rejection of Claims 20-21,25-32 and 34-36, 38 and 40 Under 35 U.S.C. 103(a)

Claims 20-21,25-32 and 34-36, 38 and 40 have been rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,925,351 (July 1999, PTO 892) in view of Hashimoto *et al* (Immunogenetics 40: 287-295, 1994; PTO 892) or Kooten *et al* (Clin Exp Immunol 110: 509-515, 1997; PTO 892) and US Pat NO. 5,653,980 (Aug 1997; PTO 892). This rejection is respectfully traversed.

The Examiner relies on the '351 patent as teaching an immunogenic composition comprising "a first polypeptide such as human or mouse lymphotoxin-p receptor fused to a second polypeptide such as the Fc domain of IgG4 immunoglobulin that are ineffective at activating complement that leads to reduction or elimination of the reference[d] fusion protein." The Examiner further states that the '351 patent further teaches that one can select a Fc domain based on whether its associated secondary effector functions are desirable for particular immune response or disease being treated with the fusion protein (See column 12, line 63-65, in particular) and soluble receptor that function as a blocking agent is useful for treating lymphocyte mediated immunological disease (See abstract, in particular)."

The Examiner relies on Hashimoto *et al* as teaching "a polypeptide such as human and mouse CD79a (Ig-a/mb-1) that is a B cell-associated antigen that forms heterodimer with CD79P to become a B cell surface receptor (See page 287, column 2, page 288, Figures 1&2, in particular)." The Examiner further states that Kooten *et al* teach that CD79 α (Ig-a/mb-1) and Ig-p (B29 or CD79 β) together forming the B cell receptor and play a critical role in the development of B cells (See page 509, column 1, first paragraph, in particular)" and that "Kooten *et al* teach that that the same receptor can be used for negative selection processes to eliminate B cells with specificity for autoantigens (See page 510, column 1, first paragraph, in particular)."

The Examiner also states that "[t]he '980 patent teaches an immunogenic composition

comprising a first polypeptide such as the CHI domain of IgE from mammalian species such as human and rat fused to a second polypeptide such as the entire sequence or part thereof of the constant CH2-CH3 domains of IgE that lacks the CHI domain from mammalian species such as human and rat and wherein the reference IgE domains are mutually exchange[d] (self versus non-self) and wherein the reference fusion polypeptide further fuses to glutathione-S-transferase (SJ26) from *Sjaponicum* which is a T helper epitope (See column 4, lines 21-26 column 9, lines 22-26, in particular)."

The Examiner states that it would have been obvious to one of ordinary skill in the art to make the claimed invention because "the '351 patent teaches that one can select a Fc domain based on whether its associated secondary effector functions are desirable for particular immune response or disease being treated with the fusion protein (See column 12, line 63-65, in particular) and soluble receptor that function as a blocking agent is useful for treating lymphocyte mediated immunological disease (See abstract, in particular)." The Examiner further states that "Hashimoto *et al* teach a polypeptide such as human and mouse CD79 α (Ig- α /mb-1) that is a B cell-associated antigen that forms heterodimer with CD79 β to become a B cell surface receptor (See page 287, column 2, page 288, Figures 1&2, in particular)." The Examiner also states that Kooten *et al* teach that the CD79 α (Ig- α /mb-1) and Ig- β (B29 or CD79 β) B cell receptor "can be used for negative selection processes to eliminate B cells with specificity for autoantigens (See page 510, column 1, first paragraph, in particular)." The Examiner continues, "[t]he '980 patent teaches that mutually exchange[d] (self versus non-self) polypeptide can enhance the immunogenicity of self polypeptide and coupling of one's own CH2-CH3 region to a non-species specific protein such as T cell epitope from *S japonicum*, one can circumvent tolerance to self polypeptide (autologous polypeptide) and give help to B-cells producing antibodies against a species specific antibodies (See column 5, lines 16-25, in particular)."

The subject matter of the pending claims and the legal requirements for establishing obviousness are set forth above. At the time the invention was made, there was no motivation to make the claimed invention, nor was there any reasonable expectation of success that one would succeed in making the claimed invention.

The '351 patent teaches compositions for developing lymphotoxin- β receptor blocking agents which can be used to block lymphotoxin- β receptor signaling. The '351 patent fails to teach or suggest the use of compositions that induce an immune response against autologous antigens. In fact, the reference teaches that "[d]eletion of the transmembrane domain is preferred over substitution with hydrophilic amino acid residues because it avoids introducing potentially

immunogenic epitopes." See column 9, lines 42-45. Accordingly, the patent actually teaches away from the use of compositions that induce an immune response. The '351 patent further teaches that LT- β receptor-Fc fusion protein described therein blocks the interaction between LT- α 1/ β 2 ligand and cell surface LT- β receptors by about 50%. The patent also teaches that the inhibition of this interaction blocks tumor cell death. Accordingly, rather than inducing an immune response against tumor cells expressing LT- β R resulting in their reduction or elimination, the compositions of the '351 patent prevent tumor cell death caused by the interaction between LT- β receptors and LT- α 1/ β 2. (see, e.g., column 13 line 56 - column 14, line 26 and Examples 3 and 4). Therefore, the compositions taught in the '351 patent do not result in the reduction or elimination of a targeted cell population. In contrast, as taught in the specification, the claimed compositions lead to killing of the cells expressing the cell surface polypeptide. Given this difference between the claimed invention and the teachings of the '351 patent, one of ordinary skill in the art would not have been motivated to modify the teachings of the reference to arrive at the claimed invention.

The other art cited by the examiner does not make up for the deficiencies of the '351 patent. As set forth above, the '980 patent teaches the use of the CH2 and CH3 domains of IgE fused to a heterologous carrier protein to stimulate an immune response to IgE. The patent further teaches that the compositions described therein are useful in binding to the free pool of IgE circulating in the body (see Column 5, lines 1-3). Therefore, the reference teaches only induction of an immune response to polypeptides in the circulation and teaches that the mechanism by which the induced auto-antibodies to IgE work is by blocking the binding of IgE to IgE α R on mast cells (see Column 5, lines 1-3). The patent further teaches that the compositions described therein are useful in binding to the free pool of IgE circulating in the body to prevent binding of that circulating IgE to the IgE α R on mast cells. The reference fails to teach compositions comprising a polypeptide expressed on the surface *B cells or activated B cells, a polypeptide specifically expressed on the surface of cells targeted for elimination or reduction*, or a molecule selected from the group consisting of: *CD79 α , CD79 β , and CD20*.

As set forth above, Hashimoto et al. teach the chromosomal localization, genomic structure, and allelic polymorphism of the human CD79 α gene. Although the reference teaches that CD79 α is expressed on B cells during certain stages of development, at the time the invention was made, there was no motivation in the art to combine the teachings of Hashimoto et al. with those of the other cited references. The '980 patent only taught enhancing immune

responses using chimeric molecules made from IgE molecules which are expressed in the circulation. IgE acts by binding to IgεR on mast cells and, as taught in the '980 patent, antibodies made against the region of self IgE that binds to the IgεR results in inhibition of binding of IgE to IgεR on mast cells. Based on these teachings with respect to the generation of antibodies against IgE molecules in the circulation and the mechanism by which such antibodies work to block binding of IgE to the IgεR on mast cells as taught in the '980 patent and the teachings of Hashimoto et al. with respect to the chromosomal localization and genomic structure of CD79α, one of ordinary skill in the art would not have been motivated to make the claimed invention. Moreover, the ordinarily skilled artisan would not have had a reasonable expectation of success in reducing or eliminating cells bearing the first polypeptide based on the teachings with respect to circulating IgE in the '980 patent.

As set forth above, Kooten et al. teach that a monoclonal antibody against Ig-β can be used to study B cell receptor signaling. In addition, the reference teaches that "[t]he combination of CD40- and antigen receptor-triggering induced strong proliferation early on, followed by massive cell death which could be prevented by IL-4." The reference states that "cross-linking of Ig-β could result in both positive and negative signals, dependent on additional signals present." Thus, in contrast to the suggestion made by the Examiner, the reference does not teach that signaling via Ig-β alone leads to negative selection of B cells. The reference further states that this represents a model for studying negative selection in mature B cells and fails to teach or suggest the use of Ig-β as a target for elimination of B cells, let alone using compositions such as those presently being claimed. Moreover, based on these teachings of the '980 patent which are limited to IgE in the circulation and the teaching of Kooten et al. that signaling via Ig-β can be either positive or negative, one of ordinary skill in the art would not have been motivated to make the claimed invention. Moreover, the ordinarily skilled artisan would not have had a reasonable expectation of success in using the claimed compositions to reduce or eliminate cells expressing Ig-β given the teachings with respect to circulatory IgE in the '980 patent. This is especially true given the teachings of the Kooten reference that signaling via Igβ is insufficient to induce negative selection in B cells in the absence of CD40 signaling and that other signals can overcome any negative signal induced by Igβ.

Accordingly, based on the teachings of the cited references, in particular on the teaching of the '351 patent that induction of an immune response to fusion proteins is not desirable in vivo and that cells are not targeted for reduction or elimination using the constructs described therein,

one of ordinary skill in the art would not have been motivated to make the claimed invention. Moreover, one of ordinary skill in the art would not have had a reasonable expectation of success that the claimed compositions would be successful in reducing or eliminating cells expressing the targeted polypeptide.

In view of the foregoing, it is respectfully requested that the rejection of claims 20-21, 25-32 and 34-36, 38 and 40 under 35 USC §103(a) be reconsidered and withdrawn.

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP

By: 

Megan E. Williams, Esq.

Reg. No. 43,270

Attorney for Applicants

28 State Street
Boston, MA 02109
(617) 227-7400
(617) 742-4214

Dated: August 22, 2003